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Mitosis mediates nuclear regulation of cancer cells under confinement

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There are number of evidences indicating that both tumour micro-environment and mechanics are playing an important role in the malignant transformation of cells and resistance to treatment. We try to take into account these important issues (micro-environment and mechanics) by developing original techniques enabling to precisely control cell micro-environment, including the applied mechanical stress. In particular, we have developed agarose-based microsystems that enable a precise control of cell micro-environment in terms of mechanics (stiffness, stress) and transport of molecules (through a porous matrix) ([1-3]). Combined with multipositions time-lapse microscopy and image analysis, we are able to decipher cell response in-situ in such confined situation, at the single cell level and over space and time.
In particular, the presence of deformed nuclei has been observed in vivo in many different type of tumour. Most studies analyzing cell response to such confined situations are limited to short periods, and little is still known about cell adaptation to prolonged squeezing, implying several cell divisions.
Using a hydrogel-based confinement system that allows the simultaneous application of different degrees of confinement, we reveal the unsuspected role of mitosis in long-term adaptation to prolonged mechanical confinement. We show that after 24h, nuclei adapt their volume to the degree of confinement by reducing their size. Surprisingly, this regulation is not linked to a slowdown in growth during cell cycle progression but occurs during confined cell division. Since confinement increases the mechanical stress within the nucleus, we use nuclear blebs as a proxy and show that this stress is also relaxed during the first mitosis under confinement, in a contractility-dependent manner. Nuclei are reaching a new homeostasis state, with no further regulation observed for the next cell generation. Using a simple geometric model, we show that the apparent surface of the nuclear envelope is the target for this new nuclear volume.
Our findings have important implications for our fundamental understanding of nuclear regulation under mechanical constraints, and should also be of primary importance in the context of cancer progression.

[1] Rivière C et al., Plaque de Micropuits En Hydrogel Biocompatible. Patent 2018:FR3079524A1
[2] A. Prunet et al., A new agarose-based microsystem to investigate cell response to prolonged confinement, Lab on a Chip. 20:4016–4030 (2020)
[3] S. Goodarzi et al., Quantifying nanotherapeutic penetration using a hydrogel-based microsystem as a new 3D in vitro platform, Lab on a Chip. 21:2495–2510 (2021)

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